REMARKS

In response to the Office Action of April 8, 2003, claims 22, 24 and 27 are amended, claims 19-21, 23 and 28-31 are canceled and new claims 32-34 are added. Claims 1, 4, 7, 19-21, 24-26 and 28-30 were rejected under 35 U.S.C. § 102 and claims 1, 4, 7 and 19-31 were rejected under 35 U.S.C. § 103(a). Each of these rejections is discussed below.

Rejections under 35 U.S.C. § 102

The Examiner has rejected claims 1, 4, 7, 19-21, 24-26 and 28-30 under 35 U.S.C. § 102 (a) as being anticipated by Nakajima *et al.* (2001) Planta Med 67:132-135, Krakauer *et al.* (2001) FEBS Letters 500:52-55, Kimura *et al.* (2001) Planta Med 67:331-334, Chi *et al.* (2001) Biochemical Pharmacology 61:1417-1427 or Chen *et al.* (2001) Biochemical Pharmacology 61:1195-1203; under 35 U.S.C. § 102(b) as being anticipated by Li *et al.* (2000) Immunopharmacology 49:295-306 or Meybeck U.S. Pat. No. 5,643,598; and under 35 U.S.C. § 102(e) as being anticipated by Xinxian, U.S. Pat. No. 6,290,995; Newmark *et al.*, U.S. Pat. No. 6,264,995; Newmark *et al.*, U.S. Pat. No. 6,391,346; Newmark *et al.*, U.S. Pat. No. 6,387,416 or Kuhrts, U.S. Pat. No. 6,475,530.

Analysis under 35 U.S.C. § 102

The Court of Appeals for the Federal Circuit has stated that anticipation requires the presence in a single prior art reference of each and every element of the claimed invention. Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co., 730 F.2d 1452, 1458 (Fed. Cir. 1984); Alco Standard Corp. v. Tennessee Valley Auth., 1 USPQ2d 1337, 1341 (Fed. Cir. 1986). "There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention." Scripps Clinic v. Genentech Inc., 18 USPQ2d 1001, 1010 (Fed. Cir. 1991, citations omitted). "To anticipate a claim, a prior art reference must disclose every limitation of the claimed invention either expressly or inherently." Atlas Powder Co. v. Ireco Inc., 190 F.3d. 1342, 1346 (Fed. Cir. (1999) (quoting In re Schreiber, 128 F.3d 1473, 1477 (Fed. Cir. 1997)). As explained in detail below, Applicant believes that the claims, as amended, are not anticipated by the prior art relied upon by the Examiner.

Rejections under 35 U.S.C. § 102(a)

The Examiner has rejected claims 1, 4, 7, 19-21, 24-26 and 28-30 under 35 U.S.C. § 102 (a) as being anticipated by Nakajima *et al.* (2001) Planta Med 67:132-135, Krakauer *et al.* (2001) FEBS Letters 500:52-55, Kimura *et al.* (2001) Planta Med 67:331-334, Chi *et al.* (2001) Biochemical Pharmacology 61:1417-1427 or Chen *et al.* (2001) Biochemical Pharmacology 61: 1417-1427. The Examiner provides that each of these references "teach that an extract from *Scutellaria baicalensis* is administered to a patient." The Examiner further provides that although Applicants argue that "the extract is being used for a different purpose other than in a method for inhibiting COX-2 . . . the fact of the matter is that each reference clearly describes that the extract is being administered to treat a COX-2 condition, i.e. treating inflammation, cancer, etc."

The Present Invention

The present invention relates generally to a method for the prevention and treatment of COX-2 mediated diseases and conditions. Claim 1 is drawn to a method for inhibiting the COX-2 enzyme by administering a composition comprised of 10% to 100% of a mixture of Free-B-Ring flavonoids. Claim 24, as amended, is drawn to a method for inhibiting the COX-2 enzyme by administering a composition comprised of 10% to 100% of a Free-B-Ring flavonoid, wherein said free-B-ring flavonoid is selected from the group consisting of baicalein, 5,6-dihydroxy-7-methoxyflavone, 7,8-dihydroxyflavone and baicalin. Support for the amendment to claim 24 can be found in Table 4 on page 25 of the Specification. New claims 33 and 34 specify that the composition is comprised of 10% to 25% of the free-B-ring flavonoid or mixtures thereof. Support for new claims 33 and 34 can be found in Example 10 and Table 8 on pages 30-32 of the Specification. As provided in the Specification, (page 4, lines 7-11), the COX-2 enzyme catalyzes two separate reactions: the metabolism of arachidonic acid to form the unstable prostaglandin G2 (PGG2), a cyclooxygenase reaction and the conversion of PGG2 to the endoperoxide PGH2, a peroxidase reaction. The short-lived PGH2 non-enzymatically degrades to PGE2. As provided in detail in the Background section of the Specification, COX-2 inhibitors are being evaluated for potential use in the prevention and treatment of a number of diseases and conditions.

The Nakajima *et al.* Reference

Nakajima *et al.* ((2001) Planta Med 67:132-135), teach the inhibition of the production of eotaxin by free-B-ring flavonoids isolated from *Scutellaria baicalensis* for the treatment of bronchial asthma. Specifically, four flavonoids isolated from *Scutellaria* root --baicalein, proxylin A, baicalin and skullcapflavon II-- were found to inhibit the production of eotaxin. Eotaxin is a protein produced by dermal fibroblasts in response to interleukin-4 and tumor necrosis factor-α and is related to bronchial diseases, such as allergies and asthma. This protein is not related to cyclooxygenase and has nothing to do with the metabolism of arachidonic acid. The inhibition of the production of eotaxin is completely unrelated to the inhibition of COX-2 activity.

Independent claim 1 of the instant invention is drawn to a method for inhibiting the COX-2 enzyme by administering a composition comprising 10% to 100% of a mixture of free-B-ring flavonoids. The Nakajima *et al.* reference does not disclose or suggest that any of the four compounds or combinations thereof, function as COX-2 inhibitors. Furthermore, there is no evidence to suggest that there would be overlap between indications requiring an inhibitor of eotaxin and those requiring a COX-2 inhibitor. In fact, there is evidence in the literature that COX inhibitors can actually induce an asthma attack. Thus, the use of a COX-2 inhibitor would actually be contraindicated for treatment of asthmatic conditions. Finally, claim 1 is drawn to a composition comprising 10% to 100% of a mixture of free-B-ring flavonoids and new claim 33 is drawn to a composition comprising 10% to 25% of a mixture of free-B-ring flavonoids. As stated above, the law is clear that to anticipate a claim, a prior art reference must disclose every limitation of the claimed invention either expressly or inherently. When a patent claims a chemical composition in terms of ranges of elements, any single prior art reference that falls within each of the ranges anticipates the claim. In the instant case, however, the Nakajima *et al.* reference provides no range for the amount of free-B-ring flavonoids in their composition. Thus, the Nakajima *et al.* reference does not expressly anticipate the claimed range. Furthermore, it cannot be concluded with any degree of certainty that the composition of the Nakajima *et al.* reference must fall within the claimed range. Thus, the Nakajima *et al.* reference does not inherently anticipate the claimed range. As such, Applicant maintains that the Nakajima *et al.* reference does not anticipate independent claim 1.

Independent claim 24 is drawn to a method for inhibiting the COX-2 enzyme by administering a composition comprised of 10% to 100% of a free-B-ring flavonoid. New claim

34 provides that the composition is comprised of 10% to 25% of a free-B-ring flavonoid. For the reasons discussed above with respect to claim 1, Applicant maintains that the Nakajima *et al.* reference does not anticipate independent claim 24.

The Krakauer *et al.* Reference

Krakauer *et al.* ((2001) FEBS Letters 500:52-55), disclose a method for the treatment of a number of diseases ranging from food poisoning and toxic shock to autoimmune diseases, by treatment with the free-B-ring flavonoid baicalin isolated from *Scutellaria baicalensis*. Krakauer *et al.* postulate that baicalin may be therapeutically useful for mitigating the pathogenic effects of staphylococcal exotoxins by inhibiting the signaling pathways activated by superantigens. There is no evidence that there is any relationship between the inhibition of the signaling pathways activated by superantigens and the inhibition of COX-2 activity.

As noted above, claim 1 of the instant invention is drawn to a method for inhibiting the COX-2 enzyme by administering a composition comprised of 10% to 100% of a mixture of free-B-ring flavonoids. The Krakauer *et al.* reference does not disclose or suggest treatment using a mixture of free-B-ring flavonoids. The Krakauer *et al.* reference also does not disclose or suggest that the free-B-ring flavonoid baicalin or any other free-B-ring flavonoid functions as COX-2 inhibitor. Furthermore, although there may be some overlap between indications requiring the inhibition of the signaling pathways activated by superantigens and those requiring a COX-2 inhibitor, there is no evidence to suggest that the overlap would be substantial. That is to say that there are likely to be diseases or conditions in which a COX-2 inhibitor would be indicated for which an inhibitor of the signaling pathways activated by superantigens would not be effective and visa versa. As stated above, the law is clear that to anticipate a claim, a prior art reference must disclose every limitation of the claimed invention either expressly or inherently. Applicant maintains that the Krakauer *et al.* reference does not anticipate independent claim 1.

For the reasons discussed above with respect to independent claim 1, Applicant also maintains that the Krakauer *et al.* reference also does not anticipate independent claim 24. Additionally, independent claim 24 is drawn to a method for inhibiting the COX-2 enzyme by administering a composition comprised of 10% to 100% of a free-B-ring flavonoid and new claim 34 provides that the composition is comprised of 10% to 25% of a free-B-ring flavonoid. As stated above, when a patent claims a chemical composition in terms of ranges of elements, any single prior art reference that fall within each of the ranges anticipates the claim. In the

instant case, however, the Krakauer *et al.* reference provides no range for the amount of free-B-ring flavonoid in their composition. Thus, the Krakauer *et al.* reference does not expressly anticipate the claimed range. Furthermore, it cannot be concluded with any degree of certainty that the composition of the Krakauer *et al.* reference falls within the claimed range. Thus, the Krakauer *et al.* reference does not inherently anticipate the claimed range. As such, Applicant maintains that the Krakauer *et al.* reference does not anticipate independent claim 24.

The Kimura *et al.* Reference

Kimura *et al.* ((2001) Planta Med 67:331-334), disclose the inhibition of adhesion molecule expression by the free-B-ring flavonoid baicalein. The baicalein was isolated from the roots of *Scutellaria baicalensis* and dissolved in ethanol to what appears to be a final concentration of less than 0.25% (Kimura *et al.*, page 332, col. 1, lines 1-3). Specifically, the free-B-ring flavonoid baicalein was found to inhibit the expression of both ELAM-1 and ICAM-1. Adhesion molecules are proteins, unrelated to both COX-2 activity and the arachidonic acid pathway. All other free-B-ring flavonoids tested including baicalin and wogonin were determined to have no effect on the inhibition of adhesion molecule expression.

Independent claim 1 of the instant invention is drawn to a method for inhibiting the COX-2 enzyme by administering a composition comprising 10% to 100% of a mixture of free-B-ring flavonoids. The Kimura *et al.* reference does not disclose or suggest a composition of matter comprised of a mixture of free-B-ring flavonoids. In fact, this reference actually teaches away from compositions comprised of mixtures of flavonoids in that only one of the nine compounds tested was actually found to be active. The Kimura *et al.* reference also does not disclose or suggest that any of these compounds function as COX-2 inhibitors. Furthermore, although there may be some overlap between indications requiring inhibition of adhesion molecule expression and those requiring a COX-2 inhibitor, there is no evidence to suggest that the overlap would be one hundred percent. That is to say that there are likely to be diseases or conditions in which a COX-2 inhibitor would be indicated for which an inhibitor of adhesion molecule expression would not be effective and visa versa. In fact, baicalin, one of the compounds determined to be inactive with respect to inhibition of adhesion molecule expression is an excellent inhibitor of COX-2 (see Specification, page 25, Table 4). In light of these comments, Applicant maintains that the Nakajima *et al.* reference does not anticipate independent claim 1.

Independent claim 24 is drawn to a method for inhibiting the COX-2 enzyme by administering a composition comprised of 10% to 100% of a free-B-ring flavonoid. New claim 34 provides that the composition is comprised of 10% to 25% of a free-B-ring flavonoid. For the reasons discussed above with respect to claim 1, Applicant maintains that the Kimura *et al.* reference also does not anticipate independent claim 24. Additionally, independent claim 24 is drawn to a method for inhibiting the COX-2 enzyme by administering a composition comprised of 10% to 100% of a free-B-ring flavonoid and new claim 34 provides that the composition is comprised of 10% to 25% of a free-B-ring flavonoid. As stated above, when a patent claims a chemical composition in terms of ranges of elements, any single prior art reference that falls within each of the ranges anticipates the claim. In the instant case, however, the Kimura *et al.* reference provides that the baicalein was dissolved in ethanol to a final concentration of less than 0.25% (Kimura *et al.*, page 332, col. 1, lines 1-3). This is not within the range of either claim 24 or 34. Thus, the Kimura *et al.* reference neither expressly nor inherently anticipates the claimed range. As such, Applicant maintains that the Kimura *et al.* reference does not anticipate independent claim 24.

The Chi *et al.* Reference

Chi *et al.* ((2001) Biochemical Pharmacology 61:1195-1203) demonstrate that wogonin, a free-B-ring flavonoid, inhibits nitric oxide (NO) as well as PGE2 production via suppression of the induction/gene expression of both iNOS and COX-2 in LPS-induced RAWcells (page, 1200, col. 1). It was also found that wogonin inhibited PGE2 production more potently than NO production. Gene expression is a measure of mRNA production from DNA. Gene expression down regulation does not necessarily lead to inhibition of the protein itself. Direct COX-2 enzyme inhibition by wogonin was not measured in this study; however, the authors speculated that in addition to the inhibition of the gene expression of COX-2, wogonin also inhibited the activity of the enzyme itself. The authors provided that although the reason for the various sensitivities to inhibition by wogonin was not known, "[i]t may be explained in part by the fact that, in addition to the suppressive effects of wogonin on iNOS and COX-2 induction, it also inhibited COX-2 activity from the homogenate of LPS-induced RAW 264.7 cells" (page 1200; col. 1). It is clear that Chi *et al.* are merely speculating that wogonin directly inhibits the COX-2 enzyme. There was no direct measurement of COX-2 enzyme inhibition activity of wogonin in

P-1202 pt. col. states that extract treat arthritis.

Chi's report and it was expressly stated that the reason for the various sensitivities was not known.

As noted above, claim 1 of the instant invention is drawn to a method for inhibiting the COX-2 enzyme by administering a composition comprised of 10% to 100% of a mixture of free-B-ring flavonoids. The Chi *et al.* reference does not disclose or suggest a composition of matter comprised of a mixture of free-B-ring flavonoids, but rather discloses the purported effect of one free-B-ring flavonoid, wogonin on COX-2 inhibition. With reference to the Specification, it can be seen that relative to the other free-B-ring flavonoids tested, such as baicalein (100% inhibition) and baicalin (97% inhibition), wogonin is actually a relatively poor COX-2 inhibitor (12% inhibition). (Specification, page 25, Table 4). As discussed in detail above, since claim 1 is drawn to a composition comprised of a mixture of free-B-ring flavonoids this claim is not anticipated by the Chi *et al.* reference.

Independent claim 24, as amended, is drawn to drawn to a method for inhibiting the COX-2 enzyme by administering a composition comprised of 10% to 100% of a free-B-ring flavonoid, wherein said free-B-ring flavonoid is selected from the group consisting of baicalein, 5,6-dihydroxy-7-methoxyflavone, 7,8-dihydroxyflavone and baicalin. Support for this amendment to claim 24 can be found in Table 4 on page 25 of the Specification. As amended, claim 24 excludes the free-B-ring flavonoid wogonin and is therefore not anticipated by the Chi *et al.* reference.

The Chen *et al.* Reference

Chen *et al.* ((2001) Biochemical Pharmacology 61:1417-1427) examined three free-B-ring flavonoids: wogonin, baicalin and baicalein for their effects on LPS-induced NO production and iNOS and COX-2 gene expression. As noted above, gene expression is a measure of mRNA production from DNA and further, gene expression down regulation does not necessarily lead to inhibition of the protein itself. In this study, Chen *et al.* also indirectly examined the effects of baicalin, baicalein and wogonin on iNOS and COX-2 enzyme activity, using a cell model of LPS stimulated prostaglandin E2 (PGE2) production, as described in Section 3.3 beginning on page 1420 of the reference. The authors conclude that "[w]ogonin, but not baicalin or baicalein, inhibited LPS-induced COX-2 expression." (Page 1426, col. 1). The authors also expressly provide that "[t]hese compounds [wogonin, baicalin and baicalein] did not affect iNOS and

COX-2 (enzyme) activity." (Page 1426, col. 1). Thus, Chen *et al.* found no direct enzyme inhibition by any of the three free-B-ring flavonoids evaluated.

As noted above, claim 1 of the instant invention is drawn to a method for inhibiting the COX-2 enzyme by administering a composition comprised of 10% to 100% of a mixture of free-B-ring flavonoids. The Chen *et al.* reference does not disclose or suggest a composition of matter comprised of a mixture of free-B-ring flavonoids. In fact, this reference clearly teaches away from the use of compositions comprised of mixtures of flavonoids for the inhibition of COX-2 in that Chen *et al.* actually reports that no direct enzyme inhibition by any of the free-B-ring flavonoids was found. As discussed in detail above, since claim 1 is drawn to a composition comprised of a mixture of free-B-ring flavonoids this claim is not anticipated by the Chen *et al.* reference.

Independent claim 24, as amended, is drawn to a method for inhibiting the COX-2 enzyme by administering a composition comprised of 10% to 100% of a free-B-ring flavonoid, wherein said free-B-ring flavonoid is selected from the group consisting of baicalein, 5,6-dihydroxy-7-methoxyflavone, 7,8-dihydroxyflavone and baicalin. As amended, claim 24 excludes the free-B-ring flavonoid wogonin and the Chen *et al.* reference expressly provides that baicalein and baicalin do not inhibit the COX-2 enzyme. Claim 24, as amended, is therefore not anticipated by the Chen *et al.* reference.

Rejections under 35 U.S.C. § 102(b)

The Examiner has rejected claims 1, 4, 7, 19-21, 24-26 and 28-30 under 35 U.S.C. § 102(b) as being anticipated by Li *et al.* (2000) Immunopharmacology 49:295-306 or Meybeck U.S. Pat. No. 5,643,598. The Examiner provides that although Applicants argue that "the extract is being used for a different purpose other than in a method for inhibiting COX-2 . . . the fact of the matter is that each reference clearly describes that the extract is being administered to treat a COX-2 condition, i.e. treating inflammation, cancer, etc." Each of these rejections is discussed below.

The Li *et al.* Reference

Li *et al.* ((2000) Immunopharmacology 49:295-306) teach the inhibition of the binding of a number of chemokines to human leukocytes via selective binding to chemokine ligands by the free-B-ring flavonoid baicalin, isolated from *Scutellaria baicalensis*. Chemokines are

chemotactic molecules that attract immune cells, helping them to "home" to sites of inflammation. Frequently, the cells producing these regulatory molecules also bear receptors for them, participating in a complex network of self-regulating and local interactions that orchestrate the proliferation of immune cells and the subsequent decline of immune activity. COX mediated inflammation pathways are downstream biological responses. Inhibition of the binding of chemokines is unrelated to the arachidonic acid metabolism by COX-2.

As noted above, claim 1 of the instant invention is drawn to a method for inhibiting the COX-2 enzyme by administering a composition comprised of 10% to 100% of a mixture of free-B-ring flavonoids. The Li *et al.* reference does not disclose or suggest using a mixture of free-B-ring flavonoids. The Li *et al.* reference also does not disclose or suggest that the free-B-ring flavonoid baicalin or any other free-B-ring flavonoid functions as a COX-2 inhibitor. Furthermore, although there may be some overlap between indications requiring an inhibitor of the binding of chemokines to human leukocytes by the free-B-ring flavonoid baicalin and those requiring a COX-2 inhibitor, there is no evidence to suggest that the overlap would be substantial. That is to say that there are likely to be diseases or conditions in which a COX-2 inhibitor would be indicated for which an inhibitor of the binding of chemokines to human leukocytes would not be effective and visa versa. As stated above, the law is clear that to anticipate a claim, a prior art reference must disclose every limitation of the claimed invention either expressly or inherently. Applicant maintains that the Li *et al.* reference does not satisfy this criterion and therefore does not anticipate independent claim 1.

For the reasons discussed above with respect to independent claim 1, Applicant maintains that the Li *et al.* reference also does not anticipate independent claim 24.

The Meybeck Reference

Meybeck (U.S. Pat. No. 5,643,598) teaches a method of formulating Scutellaria extracts or at least one active substance isolated from such extracts in liposomes for topical usage having anti-allergic, anti-inflammatory and anti-aging activity. A number of free-B-ring flavonoids, including wogonin, baicalein, scullcapflavone II and baicalin are characterized as antibacterial compounds, as described in the section entitled "Extraction and Isolation of the Antibacterial Components" (Specification, col. 6) and illustrated in Figure 2. With reference to Table II (Specification, col. 11-12), the *Scutellaria* extract in gel exhibited **no** anti-inflammatory effect (1.1%) when not incorporated into a liposome as illustrated in Figure 1, Table II (Specification,

col. 11) and as provided in the Specification (col. 12, lines 8-11). Only the liposome formulated extract had a significant anti-inflammatory effect (69.6%). A moderate effect (30.7%) was observed from the empty liposome. Thus, the Meybeck reference actually teaches away from the method of this invention with respect to the anti-inflammatory activity of these compositions. Additionally, Meybeck neither teaches nor suggests the use of free-B-ring flavonoids or mixtures thereof as COX-2 inhibitors, therefore Meybeck does not anticipate the claims of this invention, which are drawn to the inhibition of the COX-2 enzyme. Finally, the amount of free-B-ring flavonoid or mixtures thereof in the formulation taught by Meybeck is significantly less than the amount set forth in the claims. Meybeck claims a Scutellaria extract (alcoholic, aqueous or hydroalcoholic) formulated in a ratio of between 0.00001 to 2% by weight of the extract or any active substance contained in the extract, in an anti-inflammatory composition for topical applications. (Col. 6, lines 45-50). The claims of this invention are drawn to a composition comprising 10% to 100% (claims 1 and 24) or 10% to 25% (claims 33 and 34) of the free-B-ring flavonoid or mixtures thereof.

As stated above, anticipation requires the presence in a single prior art reference of each and every element of the claimed invention. For all of the reasons discussed above, Applicant maintains that the Meybeck reference does not satisfy this criterion and therefore does not anticipate independent claims 1 or 24 of the instant invention.

Rejections under 35 U.S.C. § 102 (e)

The Examiner has rejected claims 1, 4, 7, 19-21, 24-26 and 28-30 under 35 U.S.C. § 102(e) as being anticipated by Xinxian, U.S. Pat. No. 6,290,995; Newmark *et al.*, U.S. Pat. No. 6,264,995; Newmark *et al.*, U.S. Pat. No. 6,391,346; Newmark *et al.*, U.S. Pat. No. 6,387,416 or Kuhrts, U.S. Pat. No. 6,475,530. The Examiner provides that although Applicants argue that "the extract is being used for a different purpose other than in a method for inhibiting COX-2 . . . the fact of the matter is that each reference clearly describes that the extract is being administered to treat a COX-2 condition, i.e. treating inflammation, cancer, etc." Each of these rejections is discussed below.

The Xinxian Reference

Xinxian (U.S. Pat. No. 6,290,995) teaches a method for producing a pharmaceutical composition of baicalin in combination with the alkaloid berberine for use in the treatment of

cancer and control of cancer cells. Example 5 demonstrates that baicalin inhibits DNA synthesis of TPA-stimulated mouse epidermis and therefore prevents epidermis cancer (col. 6, lines 22-25). Example 6 demonstrates the effectiveness of baicalin in the treatment of gastric cancer. In this example, the mixture of baicalin and berberine is shown to inhibit levels of DNA methylation, p^{53} mutations, ^{17}p allelic loss of cancer cells and increase the function of tumor suppressor of gastric cancer cells. Example 7 demonstrates that baicalin inhibits oncogenes and Example 8 demonstrates that baicalin inhibits tumor cell proliferation and prevents tumor incidence in an animal model *in vivo*. The Xinxian patent does not teach or suggest that the free-B-ring flavonoid, baicalin, isolated from *Scutellaria baicalensis* inhibits COX-2 activity. Nor does the Xinxian patent disclose or suggest an active composition of matter comprised of a mixture of free-B-ring flavonoids. Finally, although there may be some overlap between indications requiring an inhibitor of DNA synthesis etc. and those requiring a COX-2 inhibitor, there is no evidence to suggest that the overlap would be substantial. That is to say that there are likely to be diseases or conditions in which a COX-2 inhibitor would be indicated for which an inhibitor of DNA synthesis would not be effective and visa versa. As stated above, the law is clear that to anticipate a claim, a prior art reference must disclose every limitation of the claimed invention either expressly or inherently. For all of the reasons discussed above with respect to the other references cited by the Examiner, Applicant maintains that the Xinxian reference does not anticipate independent claims 1 or 24 of the instant invention.

shows treating cancer.

The Newmark References

Newmark *et al.* (U.S. Pat. No. 6,264,995, the '995 patent), teach an herbal composition, which contains extracts from 13 different plants, including *Scutellaria baicalensis*. The patent provides that the extract reduces inflammation in bones and joints by inhibiting the COX-2 enzyme. The only definition of the *Scutellaria baicalensis* root extract is 5:1, which generally refers to 5 parts of plant root yielding one part of the extract. Considering that more than 58 compounds have been isolated from *Scutellaria baicalensis*, a hydroalcoholic extract could contain any number of compounds including, but not limited to alkaloids, benzyl alcohol glycosides, lignans, benzopyranones, amino acids, phytosterols, monosugars, flavones and flavanones. The '995 patent does not teach or suggest the use of free-B-ring flavonoids or mixtures thereof as COX-2 inhibitors. The present invention, on the other hand, discloses and claims a specific class of compounds, free-B-ring flavonoids, as having COX-2 inhibitory

all show inhibition of Cox-2.

activity. Thus, even though the Newmark *et al.* composition likely contains free-B-ring flavonoids, there is no disclosure or suggestion that these compounds are COX-2 inhibitors.

Applicant maintains that there are many advantages to isolating and identifying specific biologically active compounds from a composition of matter that could contain literally thousands of compounds. Once identified a class of compounds can be purified and concentrated to provide a more effective biological agent. Additionally, the compounds can be chemically modified to provide a composition of matter that is more active and/or less toxic. Finally, once isolated and identified a specific compound or class of compounds can be studied to determine the exact biological activity and mode of action, thus enabling more specific targeting of the compound or class of compounds for the treatment of particular diseases or conditions.

Additionally, with reference to the Table provided in the patent (col. 12), the extract of *Scutellaria baicalensis* accounted for approximately 2.6% by weight of the formulation. As discussed in detail below, the amount of free-B-ring flavonoid or mixtures thereof in the formulation taught by Newmark *et al.* is significantly less than the amount set forth in the claims of the instant invention. In the case of chemical compounds slight changes, including a mere change in the amount of a compound, have been found to be sufficient to change an old compound into a new one. (Schering Corp. v. Precision-Cosmet Co. 614 F. Supp. 1368, 1374 (D. Del. 1985)). The law is clear that new uses of known processes may be patentable. Therefore, Applicant maintains that Newmark *et al.* does not anticipate independent claims 1 and 24.

In the roots of *Scutellaria baicalensis*, the baicalin content (which accounts for approximately 80% of the total free-B-ring flavonoid content) is approximately 10% of the weight of the roots. If an average of 10% is used as a benchmark, one can obtain 10 grams of baicalin from 100 grams of dry root, assuming the extraction efficiency is 100%. With reference to the Table provided in the Newmark patent (col. 12), the *Scutellaria Baicalensis* root extract used in the formulation is a 5:1 extract, which means from 5 parts (grams/kilograms) of root, 1 part (grams/kilograms) of extract by weight is obtained. The Table further provides that the quantity of the extract used in the formulation is 20 mg. Thus, 100 mg of dry root was required to provide this amount of extract (20 mg x 5 = 100 mg dry root). Assuming for the sake of argument, that the maximum amount of baicalin/free-B-ring flavonoids was extracted, the baicalin content in the 20 mg of root extract would be approximately 10 mg. (100 mg root

extract x 10% = 10 mg baicalin in the 20 mg of root extract). Thus, the maximum purity of baicalin in the 20 mg of extract is 50%. Thus, based on the information provided in the Table, the maximum % of baicalin in Newmark's formulation is 1.3% (10 mg/770 mg total dry weight). Finally, if 20 mg of a 5:1 extract (10 mg baicalin) is administered to an average weight adult at 75 kg (165 lb) body weight, the dosage range for the extract is 0.27 mg/kg (0.14 mg/kg for baicalin). The claims of this invention are drawn to administering a free-B-ring flavonoid or mixture thereof wherein the content of said flavonoid or mixture thereof is 10% to 100% (claims 1 and 24) and 10% to 25% (claims 33 and 34) and the dosage range is 2.0 to 200 mg/kg of body weight. Therefore, the Newmark *et al.* patent does not anticipate the claims.

Newmark *et al.* (U.S. Pat. No. 6,387,416), describe an orally or topically administered composition capable of reducing inflammation. With reference to the Table (Specification col. 8-9), the maximum % of baicalin in the formulation described in this patent is approximately the same as the '995 patent discussed above. (20 mg of a 5:1 extract/760 mg total). Additionally, as discussed above Newmark *et al.* neither teach nor suggest the use of free-B-ring flavonoids as COX-2 inhibitors. Therefore, based on the reasoning above, this patent does not anticipate the claims of this invention, as amended.

Newmark *et al.* (U.S. Pat. No. 6,391,346), describe an orally administered composition capable of reducing inflammation in animals. The composition contains 13 extracts, including an extract from the plant *Scutellaria baicalensis*. The only definition of the *Scutellaria baicalensis* root extract provided in the Specification is that it is 5:1, which as noted above, generally refers to 5 parts of plant roots yielding one part of the extract. Also as noted above, considering that more than 58 compounds have been isolated from *Scutellaria baicalensis*, a hydroalcoholic extract could contain any number of compounds including, but not limited to alkaloids, benzyl alcohol glycosides, lignans, benzopyranones, amino acids, phytosterols, monosugars, flavones and flavanones. Additionally, the patent does not teach or suggest the use of free-B-ring flavonoids or mixtures thereof as COX-2 inhibitors. The extract from *Scutellaria baicalensis* accounted for approximately 12% to 18% by weight of total weight of the formulation. This amounts to a maximum of 6% to 9% by weight of free-B-ring flavonoids in the formulation. As discussed above, the claims of the instant invention provide that the free-B-ring flavonoid or mixture thereof is present in an amount greater than 10%. Therefore, based on the above reasoning, this patent does not anticipate the claims of this invention, as amended.

The Kuhrts Reference

Kuhrts (U.S. Pat. No. 6,475,530) describe weight loss compositions that combine a weight loss effective compound and a botanical COX-2 inhibitor. The plant "*Scutellaria baicalensis*" was referred to in the patent as a COX-2 inhibitor. There is no further description, however, of the material or extract of *Scutellaria baicalensis* being used. Nor is there any reference to amounts or dosage. "*Scutellaria baicalensis*" is the Latin name of a specific species of plant. It is commonly known that different parts of a plant contain totally different types of compounds in different concentrations. To date, there have been more than 58 compounds isolated from various parts of *Scutellaria baicalensis*. These compounds include alkaloids, benzyl alcohol glycosides, lignans, benzopyranones, amino acids, phytosterols, monosugars, flavones, and flavanones. The Kuhrts patent provides no examples to substantiate the claim of a COX inhibitor from *Scutellaria baicalensis*. Nor does the Kuhrts patent teach or suggest the use of free-B-ring flavonoids or mixtures thereof as COX-2 inhibitors. Therefore, for the reasons discussed above, Applicant maintains that the Kuhrts patent does not anticipate the claims of the instant invention.

Rejections under 35 U.S.C. § 103(a)

Claims 1, 4, 7 and 19-31 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Nakajima *et al.* (2001) Planta Med 67:132-135, Krakauer *et al.* (2001) FEBS Letters 500:52-55, Kimura *et al.* (2001) Planta Med 67:331-334, Chi *et al.* (2001) Biochemical Pharmacology 61:1417-1427, Chen *et al.* (2001) Biochemical Pharmacology 61: 1417-1427, Li *et al.* (2000) Immunopharmacology 49:295-306, Meybeck, U.S. Pat. No. 5,643,598, Xinxian, U.S. Pat. No. 6,290,995, Newmark *et al.*, U.S. Pat. No. 6,264,995, Newmark *et al.*, U.S. Pat. No. 6,391,346; Newmark *et al.*, U.S. Pat. No. 6,387,416 or Kuhrts, U.S. Pat. No. 6,475,530. The Examiner provides that the amounts used are simply the choice of the artisan to use in an effort to optimize the desired results.

The Examiner bears the burden of establishing a prima facie case of obviousness. In determining obviousness, one must focus on Applicant's invention as a whole. Symbol Technologies Inc. v. Opticon Inc., 19 USPQ2d 1241, 1246 (Fed. Cir. 1991). The primary inquiry is:

whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have had a reasonable likelihood of success. . . . Both

the suggestion and the expectation of success must be found in the prior art, not in the applicant's disclosure.

In re Dow Chemical, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988).

Applicant asserts that the cited references either alone or in combination, do not disclose or suggest the present invention, and therefore, do not render the present invention obvious. The present invention is drawn to a method for inhibiting the COX-2 enzyme by administering a composition comprising 10% to 100% of a free-B-ring flavonoid or mixtures thereof. The present invention implements a strategy that combines a series of biomolecular screens with a chemical dereplication process to identify active plant extracts and the particular compounds within those extracts that specifically inhibit COX-2 enzymatic activity and inflammation. A total of 1230 plant extracts were screened for their ability to inhibit the peroxidase activity associated with recombinant COX-2. This primary screen identified 22 plant extracts that were further studied for their ability to specifically and selectively inhibit COX-2 *in vitro* in both cell based and whole blood assays. Those extracts that were efficacious *in vitro* were then tested for their ability to inhibit inflammation *in vivo* using a both air pouch and topical ear-swelling models of inflammation when administered by multiple routes (IP and oral). These studies resulted in the discovery of botanical extracts that inhibited COX-2 activity and were efficacious both *in vitro* and *in vivo*. These studies also resulted in the identification of specific free-B-ring flavonoids associated with COX-2 inhibition in each of these extracts. (Specification, page 10, line 24- page 11, line 7). As discussed in detail below, Applicant asserts that the discovery of this class of COX-2 inhibitors was not motivated by the prior art relied upon by the Examiner and further that this class of COX-2 inhibitors is not rendered obvious by the art relied upon by the Examiner.

Nakajima *et al.* ((2001) Planta Med 67:132-135), teach the inhibition of the production of eotaxin by free-B-ring flavonoids isolated from *Scutellaria baicalensis* for the treatment of bronchial asthma. Specifically, four flavonoids isolated from *Scutellaria* root --baicalein, proxylin A, baicalin and skullcapflavon II-- were found to inhibit the production of eotaxin. As provided above, this protein is not related to cyclooxygenase and has nothing to do with the metabolism of arachidonic acid. The Nakajima *et al.* reference does not disclose or suggest that any of the four compounds or combinations thereof, function as COX-2 inhibitors. Furthermore, there is no evidence to suggest that there would be overlap between indications requiring an inhibitor of eotaxin and those requiring a COX-2 inhibitor. Applicant asserts therefore that one

would not be motivated by this reference to use a free-B-ring flavonoid or mixtures thereof as a COX-2 inhibitor. As stated above, both the suggestion and the expectation of success must be found in the cited reference.

Krakauer *et al.* ((2001) FEBS Letters 500:52-55), disclose a method for the treatment of a number of diseases ranging from food poisoning and toxic shock to autoimmune diseases by treatment with the free-B-ring flavonoid baicalin isolated from *Scutellaria baicalensis*. Krakauer *et al.* postulate that baicalin may be therapeutically useful for mitigating the pathogenic effects of staphylococcal exotoxins by inhibiting the signaling pathways activated by superantigens. There is no evidence that there is any relationship between the inhibition of the signaling pathways activated by superantigens and the inhibition of COX-2 activity. For the reasons stated above, Applicant asserts therefore that one would not be motivated by this reference to use a free-B-ring flavonoid or mixtures thereof as potential COX-2 inhibitors.

Kimura *et al.* ((2001) Planta Med 67:331-334), disclose the inhibition of adhesion molecule expression by the free-B-ring flavonoid baicalein. The baicalein was isolated from the roots of *Scutellaria baicalensis* and dissolved in ethanol to what appears to be a final concentration of less than 0.25% (Kimura *et al.*, page 332, col. 1, lines 1-3). Specifically, the free-B-ring flavonoid baicalein was found to inhibit the expression of both ELAM-1 and ICAM-1. All other free-B-ring flavonoids tested including baicalin and wogonin were determined to have no effect on the inhibition of adhesion molecule expression. Independent claim 1 of the instant invention is drawn to a method for inhibiting the COX-2 enzyme by administering a composition comprising 10% to 100% of a mixture of free-B-ring flavonoids. The Kimura *et al.* reference does not disclose or suggest a composition of matter comprised of a mixture of free-B-ring flavonoids. In fact, as provided above, this reference actually teaches away from compositions comprised of mixtures of flavonoids in that only one of the nine compounds tested was actually found to be active. The Kimura *et al.* reference also does not disclose or suggest that any of these compounds function as COX-2 inhibitors. In fact, baicalin, one of the compounds determined to be inactive with respect to inhibition of adhesion molecule expression is an excellent inhibitor of COX-2 (see Specification, page 25, Table 4).

Additionally, the claims of the instant invention are drawn to a method for inhibiting the COX-2 enzyme by administering a composition comprised of 10% to 100% of a free-B-ring flavonoid. The Kimura *et al.* reference provides that the baicalein was dissolved in ethanol to a final concentration of less than 0.25% (Kimura *et al.*, page 332, col. 1, lines 1-3). This is not

within the range of any of the claims of this invention. The Examiner provides, however, that the amounts used are simply the choice of the artisan to use in an effort to optimize the desired results. In response to this, however, if one does not even know that the compounds of interest are COX-2 inhibitors, one would not be motivated to optimize an unknown result by altering concentration. For the reasons discussed above, Applicant asserts therefore that one would not be motivated by this reference to use a free-B-ring flavonoid or mixtures thereof as potential COX-2 inhibitors.

Chi *et al.* ((2001) Biochemical Pharmacology 61:1195-1203) demonstrate that wogonin, a free-B-ring flavonoid, inhibits nitric oxide (NO) as well as PGE2 production via suppression of the induction/gene expression of both iNOS and COX-2 in LPS-induced RAWcells (page, 1200, col. 1). The authors provided that although the reason for the various sensitivities to inhibition by wogonin was not known, "[i]t may be explained in part by the fact that, in addition to the suppressive effects of wogonin on iNOS and COX-2 induction, it also inhibited COX-2 activity from the homogenate of LPS-induced RAW 264.7 cells" (page 1200; col. 1). As noted above, claim 1 of the instant invention is drawn to a method for inhibiting the COX-2 enzyme by administering a composition comprised of 10% to 100% of a mixture of free-B-ring flavonoids. The Chi *et al.* reference does not disclose or suggest a composition of matter comprised of a mixture of free-B-ring flavonoids, but rather discloses the purported effect of one free-B-ring flavonoid, wogonin on COX-2 inhibition. With reference to the Specification, it can be seen that relative to the other free-B-ring flavonoids tested, such as baicalein (100% inhibition) and baicalin (97% inhibition), wogonin is actually a relatively poor COX-2 inhibitor (12% inhibition). (Specification, page 25, Table 4).

Independent claim 24, as amended, is drawn to drawn to a method for inhibiting the COX-2 enzyme by administering a composition comprised of 10% to 100% of a free-B-ring flavonoid, wherein said free-B-ring flavonoid is selected from the group consisting of, baicalein, 5,6-dihydroxy-7-methoxyflavone, 7,8-dihydroxyflavone and baicalin. As amended, claim 24 excludes the free-B-ring flavonoid wogonin.

Chen *et al.* ((2001) Biochemical Pharmacology 61:1417-1427) examined three free-B-ring flavonoids: wogonin, baicalin and baicalein for their effects on LPS-induced NO production and iNOS and COX-2 gene expression. In this study, Chen *et al.* also indirectly examined the effects of baicalin, baicalein and wogonin on iNOS and COX-2 enzyme activity, using a cell model of LPS stimulated prostaglandin E2 (PGE2) production. The authors conclude that

"[w]ogonin, but not baicalin or baicalein, inhibited LPS-induced COX-2 expression." (Page 1426, col. 1). The authors also expressly provide that "[t]hese compounds [wogonin, baicalin and baicalein] did not affect iNOS and COX-2 (enzyme) activity." (Page 1426, col. 1). Thus, Chen *et al.* found no direct enzyme inhibition by any of the three free-B-ring flavonoids evaluated.

As noted above, the present invention is drawn to a method for inhibiting the COX-2 enzyme by administering a composition comprised of 10% to 100% of a free-B-ring flavonoid or mixtures thereof. The Chen *et al.* reference actually teaches away from the method of this invention in that Chen *et al.* reports that no direct enzyme inhibition by any of the free-B-ring flavonoids was found. Furthermore, when combined with the Chi reference, Applicant maintains that there would be little motivation to use a free-B-ring flavonoid or mixtures thereof as potential COX-2 inhibitors. While the Chi *et al.* reference merely speculates that wogonin inhibits the COX-2 enzyme, the Chen *et al.* reference expressly provides that there was no direct COX-2 inhibition by any of the free-B-ring flavonoids tested.

Li *et al.* ((2000) Immunopharmacology 49:295-306) teach the inhibition of the binding of a number of chemokines to human leukocytes via selective binding to chemokine ligands by the free-B-ring flavonoid baicalin, isolated from *Scutellaria baicalensis*. As noted above, inhibition of the binding of chemokines is unrelated to the arachidonic acid metabolism by COX-2. The Li *et al.* reference does not disclose or suggest using a mixture of free-B-ring flavonoids. The Li *et al.* reference also does not disclose or suggest that the free-B-ring flavonoid baicalin or any other free-B-ring flavonoid functions as a COX-2 inhibitor. Furthermore, although there may be some overlap between indications requiring an inhibitor of the binding of chemokines to human leukocytes by the free-B-ring flavonoid baicalin and those requiring a COX-2 inhibitor, there is no evidence to suggest that the overlap would be substantial. That is to say that there are likely to be diseases or conditions in which a COX-2 inhibitor would be indicated for which an inhibitor of the binding of chemokines to human leukocytes would not be effective and visa versa. For the reasons discussed above, Applicant asserts therefore that one would not be motivated by this reference to use a free-B-ring flavonoid or mixtures thereof as potential COX-2 inhibitors.

Meybeck (U.S. Pat. No. 5,643,598) teaches a method of formulating Scutellaria extracts or at least one active substance isolated from such extracts in liposomes for topical usage having anti-allergic, anti-inflammatory and anti-aging activity. A number of free-B-ring flavonoids,

including wogonin, baicalein, scullcapflavone II and baicalin are characterized as antibacterial compounds. With reference to Table II (Specification, col. 11-12), the *Scutellaria* extract in gel exhibited **no** anti-inflammatory effect (1.1%) when not incorporated into a liposome as illustrated in Figure 1, Table II (Specification, col. 11) and as provided in the Specification (col. 12, lines 8-11). Thus, the Meybeck reference actually teaches away from the method of this invention with respect to the anti-inflammatory activity of these compositions. Additionally, Meybeck neither teaches nor suggests the use of free-B-ring flavonoids or mixtures thereof as COX-2 inhibitors. Finally, the amount of free-B-ring flavonoid or mixtures thereof in the formulation taught by Meybeck is significantly less than the amount set forth in the claims. Meybeck claims a Scutellaria extract (alcoholic, aqueous or hydroalcoholic) formulated in a ratio of between 0.00001 to 2% by weight of the extract or any active substance contained in the extract, in an anti-inflammatory composition for topical applications. (Col. 6, lines 45-50). The claims of this invention are drawn to a composition comprising 10% to 100% (claims 1 and 24) or 10% to 25% (claims 33 and 34) of the free-B-ring flavonoid or mixtures thereof. As provided above, although the Examiner provides that the amounts used are simply the choice of the artisan in an effort to optimize the desired results, if one does not even know that the compounds of interest are COX-2 inhibitors, one would not be motivated to optimize an unknown result by altering concentrations.

Xinxian (U.S. Pat. No. 6,290,995) teaches a method for producing a pharmaceutical composition of baicalin for use in the treatment of cancer and control of cancer cells. Baicalin is shown to inhibit DNA synthesis, to inhibit levels of DNA methylation, p^{53} mutations, ^{17}p allelic loss of cancer cells and to inhibit oncogenes. The Xinxian patent does not teach or suggest that the free-B-ring flavonoid baicalin inhibits COX-2 activity. Nor does the Xinxian patent disclose or suggest an active composition of matter comprised of a mixture of free-B-ring flavonoids. Finally, although there may be some overlap between indications requiring an inhibitor of DNA synthesis etc. and those requiring a COX-2 inhibitor, there is no evidence to suggest that this overlap would be substantial. That is to say that there are likely to be diseases or conditions in which a COX-2 inhibitor would be indicated for which an inhibitor of DNA synthesis would not be effective and visa versa. For all of the reasons discussed above with respect to the other references cited by the Examiner, Applicant maintains that the Xinxian reference does not render the present invention obvious.

Newmark *et al.* (U.S. Pat. No. 6,264,995, the '995 patent), teach an herbal composition, which contains extracts from 13 different plants, including *Scutellaria baicalensis*. The patent provides that the extract reduces inflammation in bones and joints by inhibiting the COX-2 enzyme. The only definition of the *Scutellaria baicalensis* root extract is 5:1, which generally refers to 5 parts of plant root yielding one part of the extract. Considering that more than 58 compounds have been isolated from *Scutellaria baicalensis*, a hydroalcoholic extract could contain any number of compounds. The '995 patent does not teach or suggest the use of free-B-ring flavonoids or mixtures thereof as COX-2 inhibitors. The present invention, on the other hand, discloses and claims a specific class of compounds, free-B-ring flavonoids, as having COX-2 inhibitory activity. Thus, even though the Newmark *et al.* composition likely contains free-B-ring flavonoids, there is no disclosure or suggestion that these compounds are COX-2 inhibitors.

Applicant maintains that there are many advantages to isolating and identifying specific biologically active compounds from a composition of matter that could contain literally thousands of compounds. Once identified a class of compounds can be purified and concentrated to provide a more effective biological agent. Additionally, the compounds can be chemically modified to provide a composition of matter that is more active and/or less toxic. Finally, once isolated and identified a specific compound or class of compounds can be studied to determine the exact biological activity and mode of action, thus enabling more specific targeting of the compound or class of compounds to treatment of particular diseases or conditions. Contrary to the Examiner's assertion that optimization of factors such as concentration is standard practice, unless one knows what specific compound or class of compounds is exhibiting the desired activity, one cannot possibly optimize the concentration of that compound or class of compounds.

Newmark *et al.* (U.S. Pat. No. 6,387,416), describe an orally or topically administered composition capable of reducing inflammation. With reference to the Table (Specification col. 8-9), the maximum % of baicalin in the formulation described in this patent is approximately the same as the '995 patent discussed above. (20 mg of a 5:1 extract/760 mg total). Additionally, as discussed above Newmark *et al.* neither teach nor suggest the use of free-B-ring flavonoids as COX-2 inhibitors. Newmark *et al.* (U.S. Pat. No. 6,391,346), describe an orally administered composition capable of reducing inflammation in animals. The composition contains 13 extracts, including an extract from the plant *Scutellaria baicalensis*. The only definition of the

Scutellaria baicalensis root extract provided in the Specification is that it is 5:1, which as noted above, generally refers to 5 parts of plant roots yielding one part of the extract. Also as noted above, considering that more than 58 compounds have been isolated from *Scutellaria baicalensis*, a hydroalcoholic extract could contain any number of compounds. Additionally, the patent does not teach or suggest the use of free-B-ring flavonoids or mixtures thereof as COX-2 inhibitors. Therefore, based on the above reasoning, Applicant asserts that none of the cited Newmark *et al.* patents renders the method of the present invention obvious.

Kuhrts (U.S. Pat. No. 6,475,530) describe weight loss compositions that combine a weight loss effective compound and a botanical COX-2 inhibitor. The plant "*Scutellaria baicalensis*" was referred to in the patent as a COX-2 inhibitor. There is no further description, however, of the material or extract of *Scutellaria baicalensis* being used. Nor is there any reference to amounts or dosage. "*Scutellaria baicalensis*" is the Latin name of a specific species of plant. As a commonly known that different parts of a plant contain totally different types of compounds in different concentrations. To date, there have been more than 58 compounds isolated from various parts of *Scutellaria baicalensis*. The Kuhrts patent does not teach or suggest the use of free-B-ring flavonoids or mixtures thereof as COX-2 inhibitors. Therefore, for the reasons discussed above, Applicant maintains that the Kuhrts patent does not render the present method obvious.

Applicant maintains that none of the references cited by the Examiner, either alone or in combination render the present invention obvious. Applicant respectfully requests that this rejection be withdrawn.

Applicant believes that the pending claims are in condition for allowance. In this document, every effort has been made to address the specific rejections made by the Examiner. The undersigned believes that we are entitled to more than summary statements to refute these arguments if the Examiner is not convinced as to the patentability of the pending claims. Therefore, Applicant would appreciate it if the Examiner would specifically address Applicant's comments with respect to each individual reference. If it would be helpful to obtain favorable consideration of this case, the Examiner is encouraged to call and discuss this case with the undersigned.

This constitutes a request for any needed extension of time and an authorization to charge all fees therefore to deposit account No. 19-5117 if not otherwise specifically requested. The

undersigned hereby authorizes the charge of any fees created by the filing of this document or any deficiency of fees submitted herewith to be charged to deposit account No. 19-5117.

Respectfully submitted,

Date: July 8, 2003

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